Challenges in the Oversight of Research with Decisionally Impaired Subjects

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Dear Parent:

In previous years we have done some examinations in connection with the nutritional department of the Massachusetts Institute of Technology, with the purposes of helping to improve the nutrition of our children and to help them in general more efficiently than before.

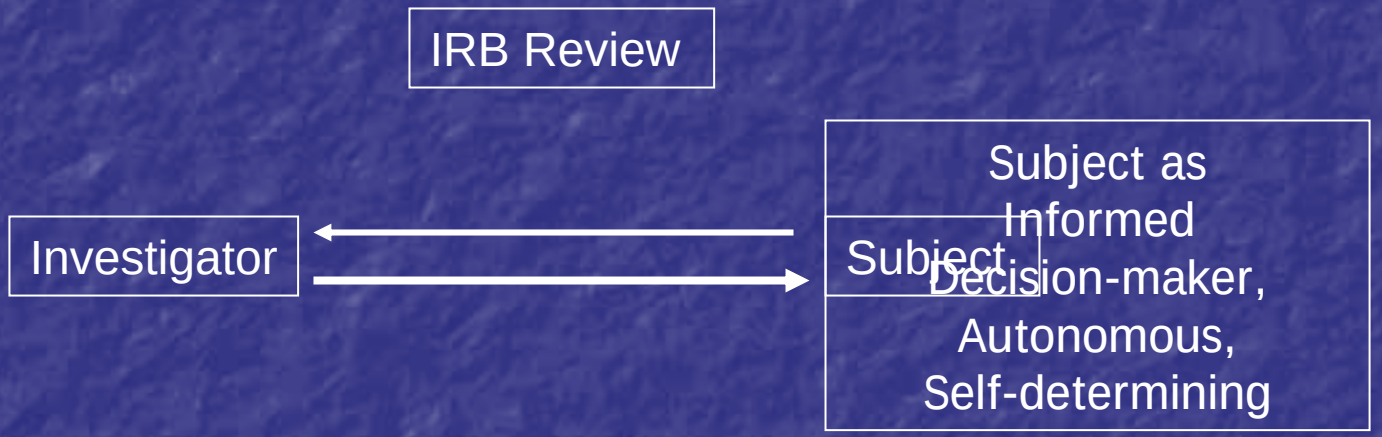
For the checking up of the children, we occasionally need to take some blood samples, which are then analyzed. The blood samples are taken after one test meal which consists of a special breakfast meal containing a certain amount of calcium. We have asked for volunteers to give a sample of blood once a month for three months, and your son has agreed to volunteer because the boys who belong to the Science Club have many additional privileges. They get a quart of milk daily during that time, and are taken to a baseball game, to the beach and to some outside dinners and they enjoy it greatly.

I hope that you have no objection that your son is voluntarily participating in this study. The first study will start on Monday, June 8th, and if you have not expressed any objections we will assume that your son may participate.

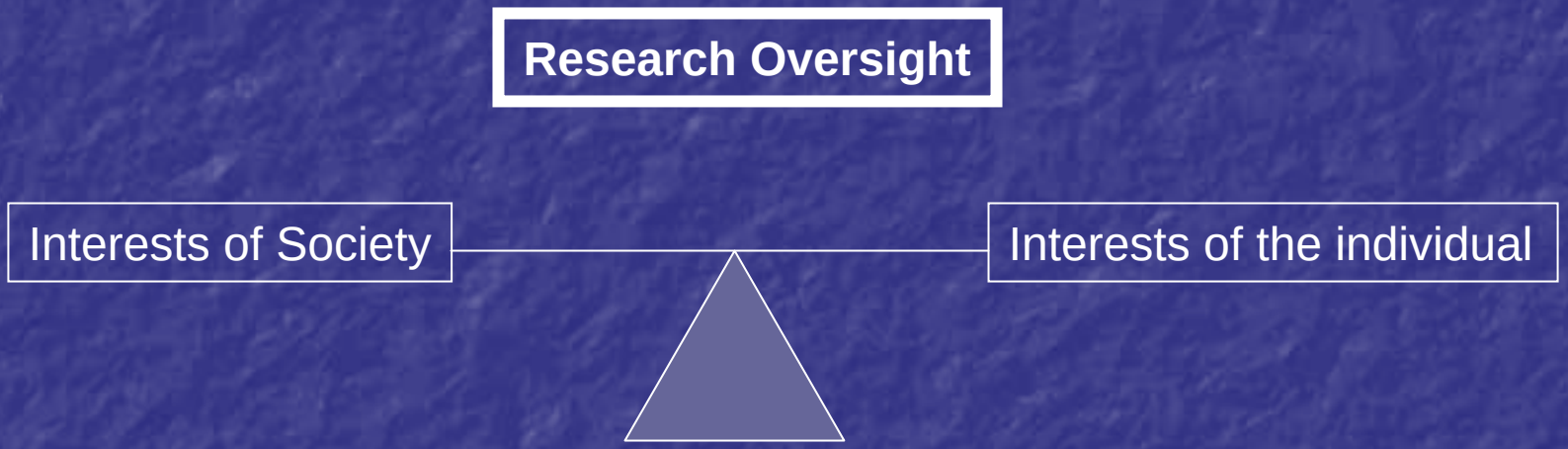
Sincerely yours,

Clemens E. Benda, M.D.

Basic Protections



...and absent the protections afforded by consent?



An ethical and practical void

- There are no federal rules which permit or properly guide research with adults who are unable to provide informed consent.
- We don’t really know the consequences of this void.

Without federal rules, is progress hindered?

- Some research questions may only be answered by research that involves persons with impaired decisionmaking capacity;
- Precluding such research would contribute to needless suffering.
- The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment.

from NIH (1999) Research Involving Individuals with Questionable Capacity to Consent: Points to Consider

“too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having”

Hans Jonas, Philosophical Reflections on Experimentation with Human Subjects (1969)

At the heart of the matter: what is “ruthless”, what is “reasonable”?

Considerations:

- The value of self-determination
- The protections we believe informed consent provides
- Our belief that the benefits of science are credible, tangible

The Regulations (and what they don't tell us)

- §46.111 Approval

  (b) When…subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included…

- Subpart B (pregnant woman, fetuses, neonates)
- Subpart C (Prisoners)
- Subpart D (Children)

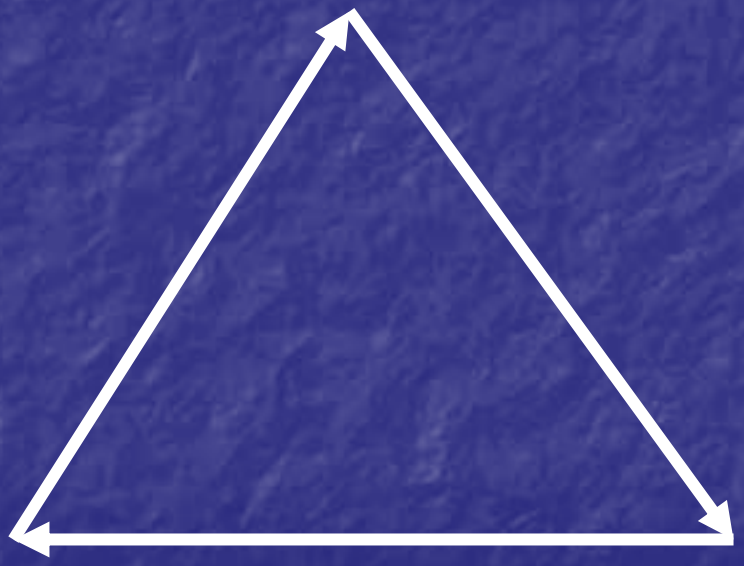
What the regs don't tell us (Cont'd)

§46.116 General requirements for informed consent.

- …the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.
- …an investigator shall seek such consent only under circumstances that provide…sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
- "Information... shall be in language understandable to the subject..."

Practical Framework

How should we define and identify those who are unable to make consent decisions (and those whose ability to consent is limited but can) ?



How should we craft a reasonable approach to risk benefit analysis when the ordinary protections provided by consent are absent?

How should we decide who may provide consent for those who are unable to consent for themselves?

Consent: principles and preconditions

- Effective disclosure of necessary information
- Understanding/Capacity
- A context in which voluntary/free choice is possible

- Able to evidence a choice
- Demonstrate factual understanding of the information
- Manipulation information rationally
- Appreciate the nature of the decision its consequences compared to other options

Intensive care unit

- In 1996, there were 5,980 ICU beds in the US, treating 55,000 patients each day.
- In 1999, 20% of all deaths (200,000) were in the ICU
- In, 2001 5.7 Million adults were admitted to ICUs

Angus DC et al Critical Care Medicine 2006
Presented by John M Luce to SACHRP 3/07

Intensive care unit

- ICU subjects are captive and vulnerable
- Critical illness occurs unexpectedly and evolves rapidly
- Most patients lack capacity to consent by any meaningful definition
- Many/most lack surrogates (depending on State)
- Surrogates themselves are likely to be overwhelmed

Luce JM et al. Am Rev Respir Crit Care Med 2004

Dimensions of decisional impairment

- Situational vs. disorder-related impairment
  (e.g. emergency room, "institutions," *vs*. stroke)

- Global vs. specific impairment
  (e.g. sedative overdose *vs.* paranoid psychosis)

- Static vs. progressive *vs*. episodic vs. time limited impairment
  (e.g. severe mental retardation *vs.* Alzheimer's disease *vs.* manic depressive disorder *vs.* TBI)

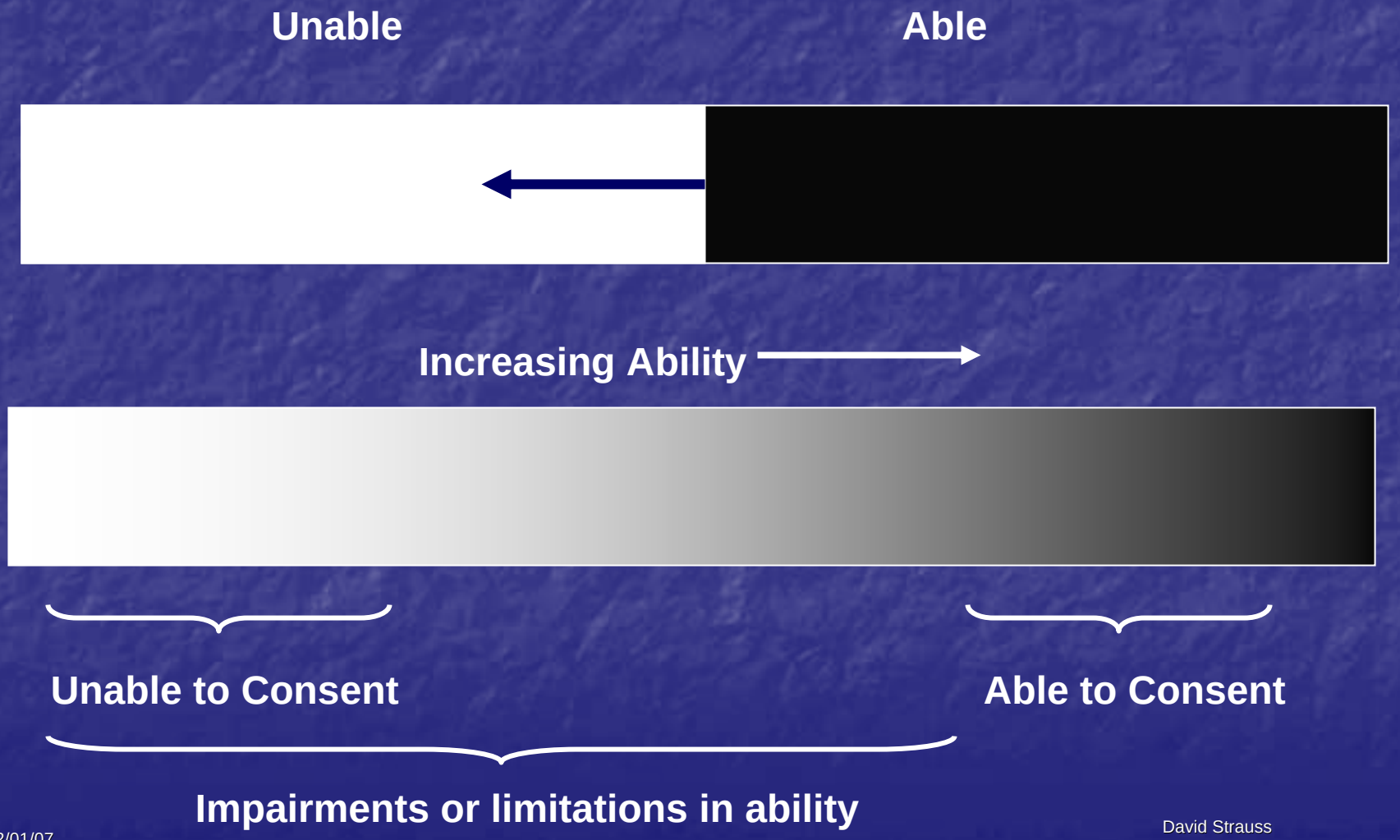
- Acute vs. persistent impairment
  (e.g. stress, or hypoxia secondary to asthma or acute pain *vs.* mental retardation or autism)

- Universal
  (e.g. therapeutic misconception, inadequate disclosure, poor health literacy)

Ability to consent?

Unable **Able**

Ability to consent occurs along a continuum



Ability is Task Specific

Decreasing Complexity 

Characteristics of Consent Decision

Hypothetical Individual's Ability re: a Range of Consent Decisions

Decreasing Complexity
Decreasing Risk
Increasing Personal Benefit

Unable to consent to higher risk/lower personal benefit research

Able to consent to lower complexity, lower risk, high benefit research (with enhancement)

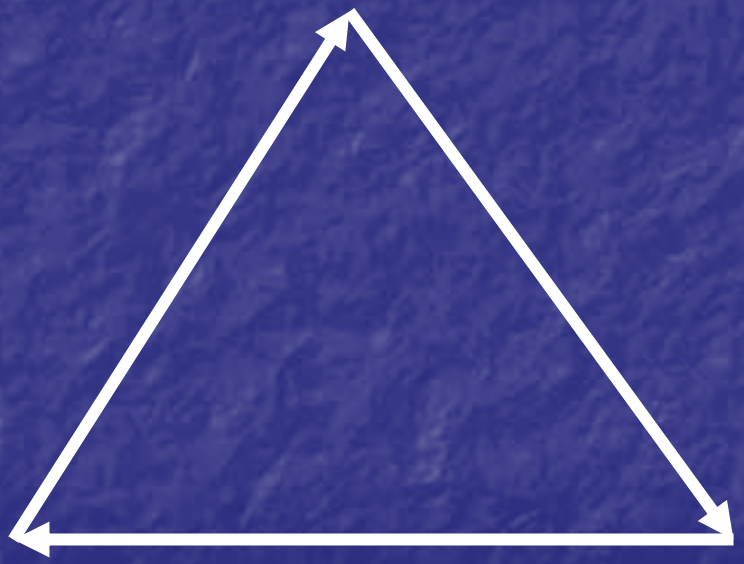
Able to appoint a proxy decision-maker

Some Practical Implications

- The subjects ability to consent should be assessed in all cases—if consent is to have meaning.
- The required assessment can be determined by an IRB and tailored to the nature and likelihood of impairment.
- There is no evident ethical, scientific, clinical or practical justification to limit protections to “individuals with mental disorders”
- Where limitations in ability to consent are present, additional consent enhancements, safeguards, and supports may be required. For those who are unable to consent, participation may only occur through an LAR.
- This assessment of capacity would serve to identify those in need of additional safeguards.

Practical Framework

How do we define and then identify those whose ability to consent is limited or those who are unable to make consent decisions?



How do we craft a reasonable approach to risk/benefit analysis when the ordinary protections provided by consent are absent?

How do we decide who may provide consent for those who are unable to consent for themselves?

- (c) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

LAR: a regulatory dead end

- The federal regulations require the subject's "legally effective informed consent"
- But, the federal regulations do not define LAR. This is left to the applicable local (State) law.
- The States, with some exceptions, have not defined LAR for research, and some do not define it at all.

Let's play "find the applicable law"
The ARDS Network Study

- Paper describes a study in which traditional mechanical ventilation was compared with ventilation at lower tidal volume in 861 patients with acute lung injury and adult respiratory distress syndrome at 11 research centers.
- Traditional ventilation was shown to be inferior.
- Mortality was reduced (39.8 vs. 31%, p=.007).
- OHRP receives letter of complaint within weeks of publication.

NEJM 2000;342:1301-8

ARDS Network Study (cont'd)

- OHRP received letter of complaint and initiates compliance investigation.
- Institutions required to support use of surrogate consent under "applicable state law".
- For 10/11 sites, OHRP accepts justification that applicable state law permits surrogate consent "for the procedures" used in the research
- One institution claimed that use of surrogate consent for clinical procedures was "standard practice" in the state. This was not considered to be consistent with federal requirements.

More regulations?

- Is a comprehensive and consistent national approach to the definition and use of “legally authorized representative” necessary (desirable?) to provide protections and promote research for those who are unable to consent?
- Options: Model State Legislation?

Practical Framework

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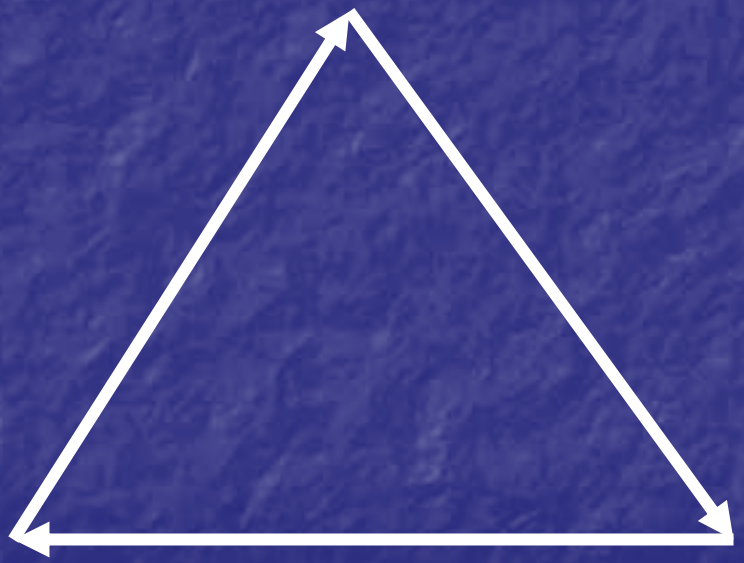

How do we decide who may provide consent for those who are unable to consent for themselves?

from Subpart A

- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

Approvability as per subpart A

Increasing Approvability →

Increasing Benefit
Decreasing Risk →

Decreasing need for external protections

Compare to Subpart D

- 404. Research not greater than minimal risk 404
- 405. Research greater than minimal risk presenting the prospect of direct benefit to the individual child subjects
- 406. Research no more than a minor increase over minimal risk, no prospect of direct benefit, likely to yield generalizable knowledge about the subject's disorder or condition.
- 407. Research not otherwise approvable (requires HHS review).

How do we define risk of harm?

Minimal

Greater than Minimal

Minor Increment

Increasing Risk

How do we define benefit?

No prospect of direct benefit

Prospect of direct benefit

Benefit →


Prospect of Direct Benefit
No Prospect
Min Risk
Minor Increment
> Min Increment

Research of considerable scientific importance and offering no direct benefit

vs.

Research of little scientific importance and offering *some* prospect of direct benefit

Approvability as per subpart A

Increasing Approvability →

Increasing Benefit
Decreasing Risk →

Decreasing need for external protections

Defining an approach

- Research risk, benefit, vulnerability and degree of decisional-impairment occur along a spectrum. A simple categorical approach to protection (as is often proposed) may not be optimal.
- Protections must be tailored to the nature and proportional to the extent of vulnerability, the magnitude of the experimental risk, and a meaningful assessment of benefit.
- Absolute thresholds and second tier reviews may create insurmountable hurdles and interfere with vitally important research.
- We must examine the consequences of change or continued failure to act.